REMARKS

Status of Claims

Claims 23 - 26 and 28 -47 remain pending in the application. Independent claims 23, 33, 37 and 43 are amended herein.

Rejections under 35 USC §112, first paragraph

In the interests of advancing prosecution, all independent claims have been amended to recite filtration through a filter series comprising **a** glass filter and **a** nylon filter" in lieu of "at least one glass filter and at least one nylon filter." However, the claims remain comprising claims and as amended are meant to the full possibility of infringement through the use of more than one glass fiber and/or more than one nylon filter.

To any extent that the examiner does not find support for "a filter series", the examiner's attention is drawn to explicit support on page 24, line 5 and 17 ([0083] and [0085] of the published application 2002/0198372) where it is recited that "the neutralized lysate was filtered in series with a nominal 0.2μm glass filter (Sartopure GF) and an absolute 0.2μm nylon filter (Pall UltiporN^{66}) (5 ft^2 each) to reduce bacterial load and endotoxin levels."

Rejections under 35 USC §103

The Examiner's §103(a) rejection of all claims over the combination of Nochumson, Wan, Lee Song and Consolazio, as well as the Pall Membrane Selection guide, is respectfully traversed. All of the independent claims are directed to methods for purification of plasmid DNA that include filtration over a glass fiber and a nylon filter together with anion exchange chromatography using a TMAE resin. The Examiner acknowledges that the references do not show the combination of TMAE chromatography with filtration through the specifically claimed nylon and glass filters.

Indeed, as acknowledged by the Examiner, although teaching TMAE anion exchange chromatography for plasmid purification, Nochumson does not teach or suggest glass fiber and

nylon filtration for removal of endotoxins. Lee does not teach or suggest static mixing or TMAE anion exchange chromatography and, while referring to filtration generally, does not teach or suggest use of glass fiber and nylon filtration in reduction of endotoxin levels. Wan is cited as teaching bacterial lysis by static mixing. However, Wan does not teach or suggest anion exchange chromatography and does not appear to mention filtration and thus cannot suggest the claimed combinations. Song teaches the theory of concentration polarization during filtration generally and does not teach or suggest any other limitations of the claims, including plasmid purification, anion exchange, filtration media, static mixing etc.

In addition to these references, none of which teach or suggest the combined use of glass fiber and nylon filtration to remove endotoxins in plasmid purification, the Examiner has cited a new reference, Consolazio, which is asserted to teach use of Pall Ultipor membrane for removal of endotoxins. The Examiner has also combined the Pall Ultipor N^{66} Membrane Filter Guide as teaching the applicability of these filters for the removal of impurities from any solution of interest, which is asserted to include a plasmid containing bacterial lysate. It is respectfully argued that no teaching or suggestion in the Consolazio nor the Membrane Filter Guide that suggests the applicability of this technology to plasmid purification or that the combination with the other references would result in the claimed invention.

Consolazio is not a combinable reference for two reasons. First, Consolazio does not teach the specific use of a combination of nylon and glass filters for endotoxin removal. The very limited teaching of Consolazio is that "removal of endotoxins from distilled water may be achieved by filtration through commercially available low porosity cellulose filters as Cuno Zetaplus filter cartridges and Pall Ultipor membrane filter cartridges. Low porosity filters of other types such as Ertel low porosity filter pads may be employed in the process." As evidenced by materials submitted in the IDS submitted herewith, Ultipor® is a Pall tradename that does not identify filter composition. Pall makes Ultipor® filters composed of glass fiber (Pall Ultipor® GF), nylon (Pall Ultipor® N6.6) and polyvinylidenedifluoride (PVDF – Pall Ultipor® VF Grade DV50 Virus Filter

Cartridges).[1] Thus, Consolazio's vague prophetic teaching that one could use Ultipor filters, among others including cellulose (both Cuno Zetaplus and Ertel), for endotoxin removal would not appraise one of skill in the art of the particular value of either glass or nylon in removal of endotoxin.

Second, Consolazio deals with the preparation of gelatin from cattle hides and is a non analogous art. In order to rely on a reference as a basis for rejection, the reference must be from an analogous art. That is, one that which is either in the field of the applicant's endeavor or is reasonably pertinent to the problem with which the inventor was concerned based on the judgment of a person having ordinary skill in the art. *See* In re Kahn, 441 F.3d 977, 987 (Fed. Cir. 2006).

The section of Consolazio dealing with removal of endotoxin is concerned with providing a source of pyrogen pure water. Removal of pyrogens from water is also completely non-analogous to removal of pyrogens from a solution containing plasmids. Purification of water which is presumably already considerably pure is not reasonably pertinent to purification of bacterial lysates, which is complex mixture. Purification of partially purified plasmid solutions is also not reasonably pertinent to purification of partially purified plasmid solutions which contain a high concentration of charged plasmid DNA molecules. The Ultipor Membrane Filtration Guide also provides no teaching or suggestion of the applicability of N_{66} to the purification of plasmid DNA. One of skill in the art would not look to the teaching of Consolazio and others relating to the purification of water to seek solutions to the purification of plasmids in aqueous solution.

The technical problem of endotoxin removal is particularly difficult as it pertains to plasmid solutions. Endotoxin is a negatively charged molecule. Thus, the prior art indicates the use of positively charged filter media to remove endotoxins. *See* Gerba and Hou, *Endotoxin Removal by Charge-Modified Filters,* Applied and Environmental Microbiology vol. 50 (6) (1985) p 1375 – 1377, submitted herewith. Plasmids represent pure strands of DNA and, by virtue of the phosphate backbone of the DNA, are also negatively charged molecules. Thus, one of skill in the

[1] The IDS submitted herewith includes a redacted copy of "Pall Solutions for the BioPharmaceutical Industry, which is submitted for the purpose of showing the different filter materials that are marketed under the Ultipor tradename.

art trying to purify plasmid DNA from a solution including endotoxins was confronted with the problem that both endotoxins and DNA are both negatively charged such that media that is able to remove one of these molecules is potentially able to remove the other as well because these molecules share charge characteristics.

The present claimed invention involves a specific combination for purification of plasmid containing solutions by filtration through a series of specific steps and including specific media including glass fiber and nylon filtration. The claimed glass fiber and nylon filters are not functioning merely as inert screens for debris and contaminants. It is believed that endotoxins are removed by binding to the glass fiber and nylon supports. Applicants surprising found that this filtration step resulted in significant purification, particularly through the removal of endotoxins, and that this step, as well as the combined method, is of particular importance in the purification of plasmid DNA at pharmaceutical scale because significant removal of plasmid DNA was not attendant to the same filtration steps that resulted in removal of endotoxin. The methods disclosed and claimed in the present application have been shown to be particularly effective in manufacturing plasmid preparations of high purity and yield at pharmaceutical scale as evidenced by commercial application and success in the field.

None of the asserted references teach use of glass and nylon filtration for endotoxin removal from plasmid DNA solutions thus providing no basis for a motivation to combine with other methodologies for this purpose. Independent claims 37 and 43 include further limitations defining plasmid purification processes that are useful for pharmaceutical scale production that include lysis by static mixing.

Conclusion

For the reasons stated herein, the Applicant respectfully submits that independent claims 23, 33, 37 and 43 are allowable and that the dependent claims are, in turn, also allowable. Applicant respectfully requests allowance of the claims at an early date. The Commissioner is authorized to charge any additional fees incurred in this application or credit any overpayment to Deposit Account No. 50-1922. Should the Examiner have any questions, please do not hesitate to call Applicant's attorney at 832-446-2421.

Respectfully submitted,

By: //mmhu// Date: July 24, 2006

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